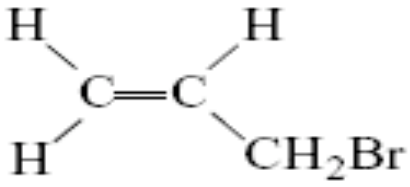
NTP
National Toxicology Program

Carcinogenicity Studies of Allyl Bromide in B6.129-Trp53^{tm1Brd} (N5) Haploinsufficient Mice

Toxicology Studies of Allyl Bromide in FVB Tg.AC Hemizygous Mice

NTP GMM 7



Allyl Bromide CAS No. 106-95-6
C_3H_5Br MW 120.99

- Nominated by NCI
- Used as a chemical intermediate in organic synthesis
  - in the manufacture of polymers/resins
  - pharmaceuticals
  - agricultural chemicals
- No previous 2-year cancer study

Allyl Bromide

- DNA binding agent *in vitro*
- Mutagenic in *S. typhimurium* TA100
- Induced unscheduled DNA synthesis in HeLa S3 cells
- Negative for micronucleated erythrocytes in mice

Study Rationale
Evaluate Mouse Models

- NTP Evaluation of genetically altered mice
  - Chemical hazard identification
  - Shorter study time (<2 yrs)
  - Fewer animals per group

Outline of Allyl Bromide Studies

2-week study

FVB/N mice - dermal

C57BL/6 mice - oral gavage

40-week study - oral gavage

FVB/N mice

C57BL/6 mice

Tg.AC mice

P53(+/-) mice

(**B6.129-Trp53^{tm1Brd} (N5) Haploinsufficient Mice**)

Selection of Doses for 2-week Studies

- Oral LD_{50} for rats: 120 mg/kg
- No reported oral LD_{50} for mice
- IP LD_{50} for mice: 108 mg/kg
- 2-week doses: 0, 7.5, 15, 30, 60, 120 mg/kg

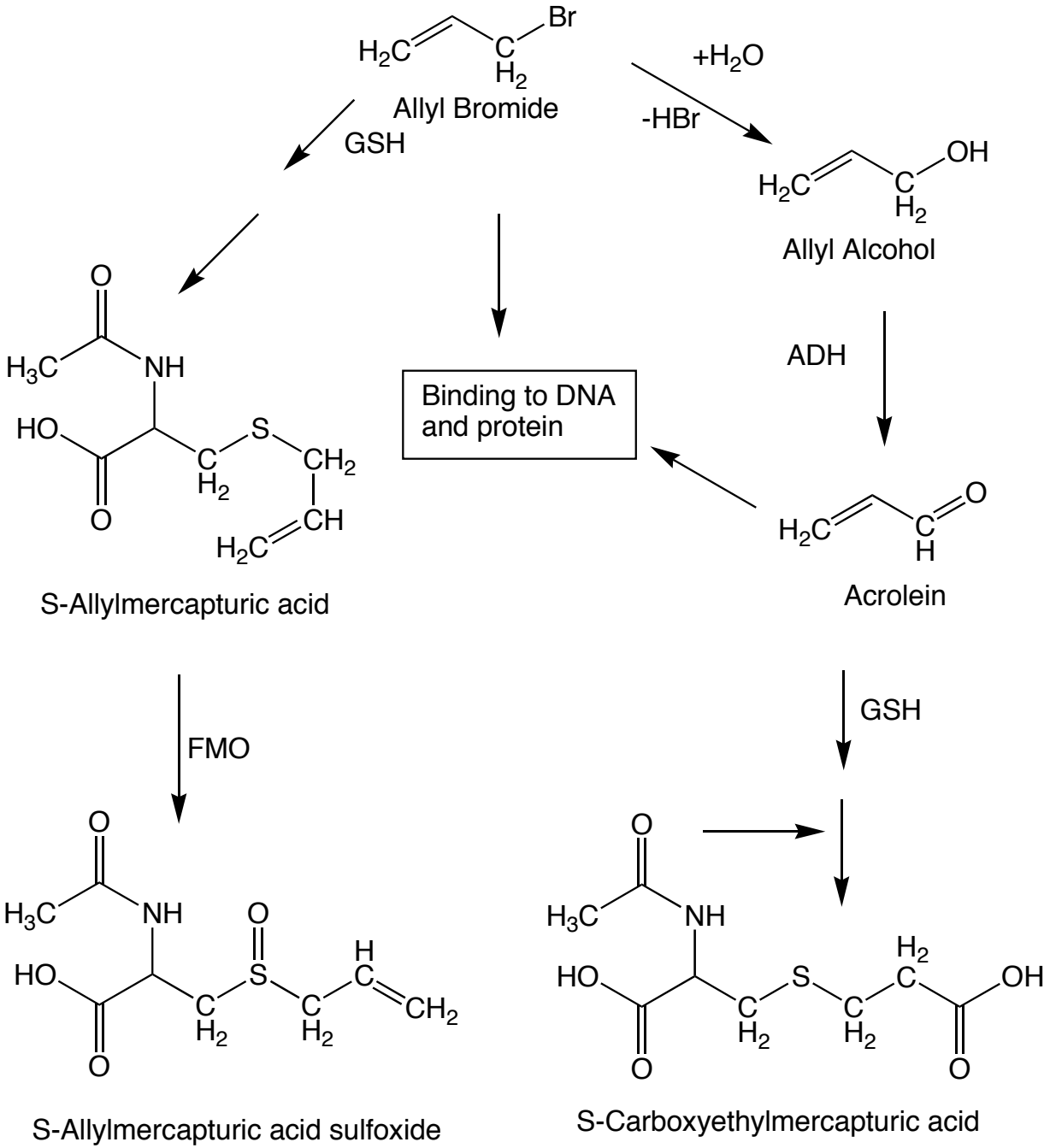
Study Design - 2 week Studies

- 2-Week dermal studies in male and female FVB/N mice
  - Chemical administered 5 days/wk in acetone to the back of shaved animals for 16 days
  - 5 animals/sex/dose; 0, 7.5, 15, 30, 60, 120 mg/kg
  - No treatment-related effects on mortality, body weight, clinical signs, or histopathologic findings
- 2-Week oral gavage study in male and female C57BL/6 mice
  - Chemical administered in corn oil 5 days/week for 16 days
  - 5 animals/sex/dose; 0, 7.5, 15, 30, 60, 120 mg/kg
  - No treatment-related effects on body weight or clinical signs
  - Forestomach toxicity seen in dosed groups

Select Results, Oral Gavage, 2-week study in C57BL/6 Mice
Survival and Forestomach Lesions

Dose (mg/kg)		0	7.5	15	30	60	120
Final Survival	Male	5	5	5	5	5	2
	Female	5	5	5	5	5	5
Epithelium, Degeneration, focal	Male	0	0	2	2	0	0
	Female	0	1	4*	5**	0	0
Epithelium, Hyperplasia, focal	Male	0	0	2	1	4*	2
	Female	0	3	4*	5**	5**	5**
Epithelium, Inflammation, focal	Male	0	0	1	3	1	0
	Female	0	0	0	2	0	0
Ulcers (epithelium)	Male	0	0	0	0	0	1
Ulcers (muscularis, serosa, epithelium)	Female	0	0	0	0	3	5**

*$p \leq 0.05$ ** $p \leq 0.01$


Allyl Bromide
GSH
+H2O
-HBr
Allyl Alcohol
ADH
Binding to DNA and protein
S-Allylmercapturic acid
Acrolein
FMO
GSH
S-Allylmercapturic acid sulfoxide
S-Carboxyethylmercapturic acid

Forestomach Toxicity
Allyl bromide, Allyl acetate, and Acrolein in Mice

Allyl bromide*	0	7.5	15	30	60	120 mg/kg
C57BL/6 mice	-	-	+	+	+	+
Allyl alcohol**	0	3	6	12	25	50 mg/kg
B6C3F1 mice	-	-	-	+	+	+
Acrolein**	0	6	1	25	50	100 mg/kg
B6C3F1mice	-	-	+	+	+	+

* 2-week studies
** 13-week studies

Dose Selection for 40-week study in Tg.AC and p53$^{(+/-)}$ Mice

- Doses selected for 40-week study based on findings in oral gavage 2-week study in C57BL/6 mice
- High dose of 8 mg/kg based on forestomach toxicity
- 40-week study conducted in male and female mice
  - Tg.AC mice at 0, 0.5, 1, 2, 4, 8 mg/kg
  - FVB mice at 0 or 8 mg/kg
  - P53$^{(+/-)}$ mice at 0, 0.5, 1, 2, 4, 8 mg/kg
  - C57BL/6 mice at 0 or 8 mg/kg
  - 15 animals/group/sex/mouse strain
  - Oral gavage in corn oil, 5 days/wk

Results of 40-week study

- No treatment related mortality, body weight effects, or clinical signs in male or female Tg.AC, FVB, $p53^{(+/-)}$, or C57BL/6 mice
- No treatment related histopathologic findings in male or female FVB, $p53^{(+/-)}$, or C57BL/6 mice or in male Tg.AC mice

Histopathologic Findings in Female Tg.AC Mice[a]

Dose (mg/kg)	0	0.5	1	2	4	8
Vulva, Squamous Cell Papilloma[b]	2* (13%)	4 (27%)	1 (7%)	6 (40%)	5 (33%)	7 (47%)
All Sites, Squamous Cell Papilloma[c]	4** (27%)	6 (40%)	3 (20%)	7 (47%)	8 (53%)	9 (60%)

[a] 15 animals per group
[b] Historical rate: 3/99 (3%)
[c] Historical rate: 43/99 (43%)
Trend Statistic: *p = 0.018 **p<0.05

Conclusions

- *No evidence of carcinogenic activity* in male or female p53 haploinsufficient mice administered allyl bromide at 0, 0.5, 2, 4, or 8 mg/kg by corn oil gavage, 5 days a week for 40 weeks
- *Marginal increase in the incidence of squamous cell papillomas*, primarily of the vulva, in female Tg.AC mice administered allyl bromide by corn oil gavage for 40 weeks